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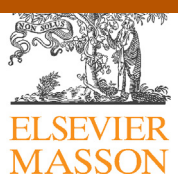

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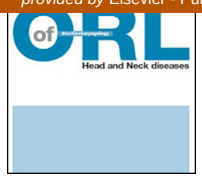

REVIEW

First bite syndrome

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Summary Based on a review of the indexed medical literature (PubMed database), the authors describe the clinical features leading to the diagnosis of first bite syndrome, the pathophysiology of this syndrome and analyse the various treatment options available to otorhinolaryngologists to manage this syndrome.

Introduction

A Google search using the terms ''first bite syndrome'' retrieved several tens of thousands of responses, about two-thirds of which corresponded to questions from patients and/or practitioners confused by this disease. This large number of search results contrasts with the small number of articles published in the medical literature, as less than 25 articles were found in the PubMed database [1—22]. In view of this discrepancy between the high demand and the poor supply, we conducted a review of the literature to define the clinical features suggestive of the diagnosis of first bite syndrome, describe the pathophysiological hypotheses proposed to explain the development of this syndrome and analyse the treatment options currently available to oto-rhinolaryngologists to manage this syndrome.

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Diagnosis

The term ''first bite syndrome'' was first used in the indexed medical literature by a North American gastroenterologist Dr W.S. Haubrich in 1986 [1] in an article published in the *Henry Ford Hospital Medical Journal* describing clinical features characterized by the occasional onset, without prodromal symptoms, at the first bite, of pharyngeal blockage of the food bolus, sometimes accompanied by retrosternal chest pain [1]. Intrigued by this painful dysphagia, which, according to him had not been previously described in medical textbooks of the time devoted to oesophageal diseases, Haubrich retrospectively reviewed the cohort of 949 patients seen between 1983 and 1985. He then discovered that all patients experiencing these symptoms presented an associated oesophageal disease (sliding hiatal hernia in 17 cases, Schatzki B rings in three cases, cancer of the oesophagogastric junction in three cases and tertiary contractions of the distal oesophagus in one case). In the light of these findings, Haubrich proposed transient oesophageal spasm as the pathophysiological basis for this syndrome [1].

This paper was the only article on this subject until 1998, when a North American otorhinolaryngologist, Dr. James

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L. Netterville [2] again used this term. In an article devoted to paragangliomas of the vagus nerve and their treatment, Netterville described an early postoperative pain syndrome (totally unrelated to the clinical features described by Haubrich [1]), characterized by sudden onset without prodromal symptoms, at the first bite, of pain or severe cramping in the ipsilateral parotid region. The patient may even avoid eating due to the severity of this syndrome. The pain, which gradually resolves with the following mouthfuls, recurs at each meal and is accentuated by the use of sialogogues. In all cases of the series reported by Netterville et al. [2], this syndrome was associated with a lesion of the ipsilateral cervical sympathetic trunk lesion. However, well before this publication, Gardner and Abdullah [23], in 1955, had already clearly described these symptoms in a study that analysed the differences between pre- and postganglionic cervical sympathectomy (superior cervical ganglion) in the treatment of certain vascular or atrophic brain lesions.

Following this publication by Netterville et al. [2], several papers concerning first bite syndrome [3—22] (Table 1) reported sudden onset of intense head and neck pain in the parotid region, with no prodromal symptoms. Pain was triggered by the first bite and then gradually resolved with subsequent bites. However, several clinical variants were reported. For example, the syndrome can occur several months rather than several days after upper neck surgery [4] and the pain can also be located in the mandibular region or oral cavity and radiate to the ear [12]. Some authors [11,13,14,18,20] have reported that pain can also be triggered by salivation, simply thinking about a meal or by simple contact with various foods even in the absence of chewing. An associated cervical sympathetic trunk lesion was present in only 42.8% of the 112 cases published (Table 1) since the article by Netterville et al. [2]. Two main aetiological classes can be distinguished: postoperative syndromes and tumours. More than 95% of published cases correspond to postoperative syndromes [1—14,18—21] (Table 1) following upper neck surgery (resection of mixed and/or cervical sympathetic nerve tumours, deep cervical lymph node dissection, parotid gland surgery, particularly involving the deep lobe of the parotid gland, parapharyngeal and infratemporal fossa surgery, carotid bifurcation and/or internal carotid artery surgery, resection of the styloid process). Tumours responsible for first bite syndrome were malignant in all cases arising from the deep lobe of the parotid gland, parapharyngeal space or ipsilateral submandibular gland and, in a few cases, the tumour was detected on conventional imaging only several months after onset of the pain [15—17,22].

All authors agree that the positive diagnosis is exclusively clinical, based on the findings of clinical interview and a normal physical examination [2—20]. However, several differential diagnoses must be eliminated. The leading differential diagnosis is temporomandibular joint dysfunction, which can be easily distinguished, as first bite syndrome is not associated with pain or discomfort on mobilization and palpation of the ipsilateral temporomandibular joint. The second differential diagnosis is gastro-oesophageal reflux, which can also be easily excluded in the absence of pain in the parotid region and the presence of associated digestive and pharyngeal signs. Glossopharyngeal neuralgia, triggered by ipsilateral intraoral palpation of the subtonsillar region,

Table 1 Aetiologies and symptoms associated with first bite syndrome (PubMed meta-analysis).

Authors	Year	N	Aetiology	Associated symptoms
Series				
Netterville et al. [2]	1998	9	PO	9 cases of cervical sympathetic trunk injury
Chiu et al. [3]	2002	12	PO	6 cases of cervical sympathetic trunk injury
Kawashima et al. [7]	2009	9	PO	3 cases of cervical sympathetic trunk injury
Linkow et al. [19]	2012	45	PO	10 cases of cervical sympathetic trunk injury
Abdeldaoui et al. [20]	2013	17	PO	12 cases of cervical sympathetic trunk injury
Case reports				
Cernea [4]	2006	1	PO	—
Kamal et al. [5]	2007	1	PO	Cervical sympathetic trunk injury
Ali et al. [6]	2008	1	PO	Cervical sympathetic trunk injury
Mandel and Syrop [8]	2008	1	PO	Cervical sympathetic trunk injury
Borras Pereira et al. [9]	2009	1	PO	Cervical sympathetic trunk injury
Casserly et al. [10]	2009	1	PO	Cervical sympathetic trunk injury
Lee et al. [11]	2009	5	PO	2 cases of cervical sympathetic trunk injury
Philips and Farquhar-Smith [12]	2009	1	PO	—
Albasri et al. [13]	2009	2	PO	—
Costa et al. [14]	2011	2	PO	—
Deganello et al. [15]	2011	1	T	—
Dierk et al. [16]	2011	1	T	—
Liberman and Har-El [17]	2011	1	T	Cervical sympathetic trunk injury
Wong et al. [18]	2011	1	PO	—
Simms et al. [21]	2012	3	PO	—
Guss et al. [22]	2012	1	T	—

N: number; PO: postoperative; T: tumour.

and Eagle's syndrome or stylalgia do not raise any real diagnostic problems, as the pain in these syndromes is not related to eating and is triggered by palpation (external or intraoral) of the styloid process, greater cornu of the hyoid bone and/or stylohyoid ligaments. No complementary investigation is required when this syndrome occurs during the days following neck surgery. In contrast, in the absence of a history of ipsilateral upper neck surgery, an imaging assessment should be performed to exclude a cancer of the deep lobe of the parotid gland, submandibular gland or ipsilateral parapharyngeal space and imaging should be repeated, as the tumour may only become visible several months after onset of the pain [15—17,22].

Pathophysiology

According to Netterville et al. [2], first bite syndrome is secondary to loss of sympathetic innervation to the ipsilateral parotid gland. This loss of innervation would lead to denervation of sympathetic receptors located on parotid myoepithelial cells. These cells, which also possess parasympathetic receptors, then become hypersensitive to parasympathetic stimulation, resulting in a very intense (supramaximal) contractile response at the first bite, inducing the head and neck pain and/or cramps experienced and described by the patients [2]. This pathogenic hypothesis, also proposed by Chiu et al. [3] and by Kawashima et al. [7], explains all aetiologies of first bite syndrome. A direct injury to the cervical sympathetic trunk (cranial nerve surgery at the skull base and parapharyngeal space, deep cervical lymph node dissection, tumours), or postganglionic sympathetic efferents of the cervical sympathetic trunk, corresponding to the pericarotid sympathetic plexus (styloid process surgery, carotid surgery, parotid surgery with ligation of the external carotid artery, tumours) would therefore be the cause of this syndrome. In this context, Gardner and Abdullah [23], as well as Kawashima et al. [7], highlighted the importance of the level of cervical sympathetic trunk lesion. According to these authors, factors predisposing to the development of first bite syndrome are: (a) preservation or injury to the superior cervical ganglion (in the case of cervical sympathetic trunk lesions), which would explain why all patients who underwent resection of the cervical sympathetic trunk without excision of this ganglion did not develop first bite syndrome or (b) ligation or resection of part of the external carotid artery and damage to the surrounding sympathetic plexus.

This attractive aetiological mechanism corresponding to imbalance between parasympathetic and sympathetic innervation of myoepithelial cells of the parotid gland, has also been proposed to explain non-surgical forms of first bite syndrome due to a malignant tumour of the parotid gland and/or ipsilateral parapharyngeal space [15,16]. In this context, first bite syndrome would be related to parotid parasympathetic denervation caused by the tumour associated with sympathetic irritation secondary to compression and/or tumour invasion of the pericarotid sympathetic plexus in the intra parotid portion of the external carotid artery.

Without refuting these pathophysiological mechanisms and although two retrospective studies [19,20] based on cohorts of more than 100 consecutive patients undergoing surgery of the infratemporal fossa, parotid gland and/or parapharyngeal space, reported an almost identical incidence of 10% of this still little known syndrome, it would appear that, in view of the extreme rarity of this syndrome compared to the relatively high rate of external carotid artery and/or parotid gland surgery with ligation or resection of the external carotid artery, sympathetic-parasympathetic conflict on myoepithelial cells of the parotid gland is probably not the only mechanism involved in the pathogenesis of this syndrome, whose pathophysiology has not yet been fully elucidated.

Treatment

Various treatment strategies (Table 2) have been proposed to relieve the pain of first bite syndrome. Non-steroidal anti-inflammatory drugs, acupuncture, anaesthetic sprays or local anaesthetic block and oral analgesics such as paracetamol, codeine or narcotics, and tympanic neurectomy or auriculotemporal neurectomy have not been demonstrated to be effective. Anticonvulsants (carbamazepine, pregabalin, gabapentin) used alone or in combination with tricyclic antidepressants (amitriptyline) can decrease the severity and/or duration of the pain (Table 3).

However, several other treatment options appear to be effective, confirming the role of the parotid gland in the pathogenesis of this syndrome. For example, parotidectomy performed in the context of first bite syndrome revealing a malignant tumour constantly relieves the pain [15—17]. However, parotidectomy must be as complete as possible, as first bite syndrome is also a complication of partial parotid gland surgery, particularly when it only involves the deep lobe of the gland [19].

Similarly, several authors [15,19,20] have reported that neoadjuvant radiotherapy can lead to resolution of postoperative first bite syndrome following neck lymph node dissection. The study conducted by Hakim et al. [23] on rabbit lacrimal myoepithelial cells, which have a very similar structure to parotid myoepithelial cells, helps to explain the efficacy of radiotherapy which, from a dose of 15 Gray, induces loss of alpha-smooth muscle actin (alpha-SMA) associated with rarefaction and condensation of myofilaments [24]. Before considering this type of ''radical'' treatment, which is not devoid of risks and/or functional sequelae, it must be remembered that (a) in a large proportion of cases of first bite syndrome, the severity of the symptoms decreases with time and pain sometimes completely disappears after several months to one year [3,5,13,14,18,20] and (b) intraparotid injection of botulinum toxin is always effective both in terms of analgesia and improvement of quality of life [6,11]. Botulinum toxin injection is performed over the painful zone in the parotid gland. A standard method has not yet been defined and the protocol varies from three successive injections of 11 units [11] to a single injection of 75 units [6]. The initial efficacy is maintained for six months after the injection of 75 units, while first bite syndrome recurred in four of the five patients treated with 33 units in three injections. However, a single injection of 75 units is also much more painful [6,11].

Table 2 Treatment of first bite syndrome.

Authors	N	Treatment	Effective
Series			
Netterville et al. [2]	9	Auriculotemporal nerve section-resection (1)	NS
Chiu et al. [3]	12	Spontaneous improvement (1)	Yes
		Radiotherapy (1)	Yes
		NSAID (6), carbamazepine (1), tympanic neurectomy (3)	No
Kawashima et al. [7]	9	NS	NS
Linkow et al. [19]	45	NS	NS
Abdeldaoui et al. [20]	17	Analgesics, carbamazepine, gabapentin pregabalin (14)	Partial
		Radiotherapy (1)	Yes
		Spontaneous resolution (2)	–
Case reports			
Cernea et al. [4]	1	Carbamazepine	Yes
Kamal et al. [5]	1	Spontaneous resolution	–
Ali et al. [6]	1	Acupuncture, various analgesics + various neurotropic agents, tympanic neurectomy	No
		Parotid botulinum toxin injection	Yes
Mandel and Syrop [8]	1	Various analgesics	No
Borras Pereira et al. [9]	1	Carbamazepine	No
Casserly et al. [10]	1	Pregabalin	No
Lee [11]	5	Parotid botulinum toxin injection	Yes
Philips et al. and Farquhar-Smith [12]	1	Various analgesics	No
Albasri et al. [13]	2	Spontaneous resolution (1)	–
		Analgesics, carbamazepine, gabapentin	No
Costa et al. [14]	2	Non-steroidal anti-inflammatory drugs (1)	No
		Radiotherapy (2)	Yes
Deganello et al. [15]	1	Tumour resection	Yes
Diercks et al. [16]	1	Tumour resection	Yes
Liberman and Har-El [17]	1	Tumour resection	Yes
Wong et al. [18]	1	Spontaneous resolution	–
Simms et al. [21]	3	Botulinum toxin injection	Yes
Guss et al. [22]	1	Tumour resection	Yes

N: number; NS: not specified.

Table 3 Syndromes reflecting cervical sympathetic trunk injury.

Syndromes	Symptoms	Pathogenesis suggested
Horner	Myosis, ptosis, enophthalmos, hemifacial anhidrosis	Deficient-destructive sympathetic trunk lesion
Pourtour du Petit	Mydriasis, eyelid retraction, exophthalmos, hemifacial hyperhidrosis	Irritating-hyperactive sympathetic trunk lesion
Frey	Lateral head and neck erythema and excessive sweating triggered by eating	Aberrant sympathetic-parasympathetic sprouting
Harlequin	Erythema and hemifacial hyperhidrosis	Cervical sympathetic vasomotor and sudomotor nerve lesions
First bite	Intense parotid pain at the first bite	Intraparotid sympathetic deafferentation and parasympathetic reafferentation

Conclusion

Like Harlequin syndrome, Frey's syndrome, Horner's syndrome or Pourtour du Petit (French military surgeon who described this syndrome during the Napoleonic wars), syndrome corresponding to the inverse of Horner's syndrome [25], first bite syndrome is due to sympathetic-parasympathetic dysfunction in the head and neck (Table 3). Otorhinolaryngologists must be familiar with this syndrome in order to detect it following head and neck surgery (particularly surgery involving the deep lobe of the parotid gland or the cervical sympathetic trunk), and to also recognise it as a possible sign of malignant tumour of the deep lobe of the parotid gland, submandibular gland or ipsilateral parapharyngeal space. Although the pain sometimes resolves spontaneously, it is often disabling and the recently described intraparotid botulinum toxin injection [6,11,22] appears to be the most effective first-line treatment option at the present time, although the injection protocol (number of injections and total dose injected) and its long-term efficacy have not yet been clearly defined. Finally and with a current incidence of 10% following upper neck surgery (particularly involving the deep lobe of the parotid gland or the cervical sympathetic trunk) [19], it is essential to inform the patient before the operation about the risk of this post-operative syndrome, especially when surgery is not formally indicated, in order to strictly comply with current legislation [26] and avoid any subsequent medicolegal problems.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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